REMARKS

I. The Office Action

Claims 28-48 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Claims 28-38, 43, 44, 47, and 48 were rejected under 35 U.S.C. § 103(a) for allegedly being obvious over U.S. Patent 4,792,447 ("the Uhr patent") taken with International Patent Publication WO 03/004056 ("the Raison publication") and Abe et al., *Am. J. Clin. Path.*, *100*, 67-74 (1993) ("the Abe reference"). The Office also rejected claims 39-42, 45, and 46 under 35 U.S.C. § 103(a) for allegedly being obvious in view of the Uhr patent, the Raison publication, and the Abe reference taken with U.S. Patent Publication No. US 2005/0255532 ("the Ruben publication"). Reconsideration of the rejections is respectfully requested.

II. Amendments to the Claims

Claims 28, 33, 38, 40, 43, 47, and 48 have been amended to recite that the anti-LMA antibody or LMA ligand conjugate does not bind Ig lambda light chain associated with an Ig heavy chain. The amendment is supported by the specification at, e.g., page 42, lines 18-26. No new matter has been added by way of these amendments.

III. The Rejection Under 35 U.S.C. § 112, first paragraph, Should Be Withdrawn.

Claims 28-48 were rejected for allegedly failing to satisfy the written description requirement of Section 112, first paragraph, because the specification allegedly does not provide sufficient written description for an anti-LMA antibody that "does not bind light chain associated with a heavy chain." Applicants respectfully disagree. However, solely in an effort to advance prosecution of the application, claims 28, 33, 38, 40, 43, 47, and 48 have been amended to recite that the anti-LMA antibody or LMA ligand conjugate does not bind Ig lambda light chain associated with an Ig heavy chain, as supported by the specification at, e.g., page 42, lines 18-26. Applicants respectfully request withdrawal of the rejection under Section 112, first paragraph.

IV. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn.

The Office rejected claims 28-38, 43, 44, 47, and 48 under Section 103(a) for allegedly being obvious in view of the Uhr patent taken with the Raison publication and the Abe reference. Claims 39-42, 45, and 46 were rejected for allegedly being obvious in view of the Uhr patent, the Raison publication, and the Abe reference further in view of the Ruben publication. The rejection is respectfully traversed for the reasons set forth below. As part of the response to the Office Action, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 of Cameron Jennings, Ph.D., a scientist whose experience in the field qualifies him to comment on what one of ordinary skill in the art would have understood and predicted from the cited art in February 2004 (i.e., the effective filing date of the instant application). (See Rule 132 Declaration at paragraphs 1-11.)

The pending claims are directed, at least in part, to a method for the treatment or prophylaxis of a B-cell disorder in a subject or inhibiting the growth or killing lymphoid cells in a subject. The method comprises administering to the subject an anti-LMA antibody or an LMA ligand to inhibit the growth of, or kill, lymphoid cells in the subject (claims 28 and 33). The pending claims also provide a method for autologous hematopoietic cell transplantation in a subject, the method comprising removing a hematopoietic progenitor cell population from the subject, treating the cell population with an anti-LMA antibody or LMA ligand conjugate, and transplanting the treated cell population into the subject (claim 38). The anti-LMA antibody and LMA ligand specifically bind LMA and do not bind Ig lambda light chain associated with an Ig heavy chain.

The Office asserted that the Uhr patent discusses antibodies against lambda light chain associated with intact immunoglobulins, but acknowledged that the patent does not disclose an antibody that binds free lambda light chain. The Uhr antibodies purportedly are conjugated to a toxin, which the Office alleges is a "detectable moiety," and can be used to treat B cell tumors. The Raison publication is cited as disclosing that myeloma cells can produce either kappa or lambda light chain, that kappa light chain is expressed on the surface of kappa myeloma cells, and that antibodies to kappa light chain can be used to treat such tumors. Abe et al. is cited as disclosing antibodies which bind free light chain that is not associated with intact immunoglobulin. According to the Office, the claimed subject matter is obvious because "it would have been expected by a routineer that lambda light chain

expressing myeloma cells would have been found which express free lambda light chain on the cell surface" (Office Action, page 4). Applicants respectfully disagree; the expression of the kappa light chain in myeloma cells is in no way predictive of (i) the expression and (ii) localization of (iii) free lambda light chains in malignant B cells because the structure and other properties of these two molecules are different and were known to be different as of the effective filing date of the application. (See Rule 132 Declaration at paragraph 13.) Because it was not predictable that free lambda light chains would be localized on malignant B-cells, there is no predictable basis in the cited references for, e.g., administering an anti-LMA antibody to inhibit the growth of, or kill, lymphoid cells or treating a hematopoietic progenitor cell population with the anti-LMA antibody or LMA ligand.

As a preliminary matter, there is nothing inherent in the structure of lambda light chains that suggests that the proteins are incorporated into cell membranes. (See Rule 132 Declaration at paragraph 17.) Light chains are composed, in part, of seven beta strands that form a sandwich of two beta sheets. This structural motif is found on a vast array of protein sub-families with diverse biological activities and sub-cellular locations. Kappa and lambda light chains do not contain structural motifs that would suggest that free light chains are localized to the cell membrane, there is no membrane targeting sequence found in light chain proteins, and no normal biological function has been attributed to light chains alone (i.e., in the absence of immunoglobulin heavy chains). (See Rule 132 Declaration at paragraph 17.)

Further, the membrane interaction of kappa light chains occurs via hydrophobic and/or electrostatic interactions, and kappa light chain expression on B-cells is not predictive of free lambda light chain localization due to differences in lambda light chain structure that mediate hydrophobic and/or electrostatic interactions. (See Rule 132 Declaration at paragraph 21.) As explained by Dr. Jennings in the Rule 132 declaration, the kappa and lambda genes differ in the number and general arrangement of variable (V), joining (J) and constant (C) genes. (See Rule 132 Declaration at paragraph 14.) For example, there is a single C kappa gene while there are five functional C lambda genes. (*Id.*) In addition to comprising different arrangements of V, J, and C domains, the amino acid sequences *within* the regions differ. Kappa and lambda proteins share minimal sequence identity within their C domains. (*Id.* at paragraph 15.) Additionally, genetic recombination

events and somatic hypermutation results in variability in the V domains of kappa and lambda light chains. (*Id.*) The differences in the primary structure of kappa and lambda light chains is significant, as highlighted by the divergence in processes used to force "strand switching" in kappa and lambda light chains. (*Id.* at paragraph 16.) The "strand switch" phenomenon is dependent on local structure, and confirms the variability in sequence, structure, and biological function between the two immunoglobulin light chains. (*Id.*) The distinct structure of kappa and lambda light chains is further evinced by the selective binding of the *Peptostreptococcus magnus* protein L to kappa light chains and *not* lambda light chains. (*Id.* at paragraph 18.)

The differences in primary structure of free kappa and lambda light chains affect not only the charge of the exposed side chains of the proteins, but also the proteins' tendency to form monomers (kappa light chains) or dimers (lambda light chains). The proteins' structural differences yield different pathological conditions. (*Id.* at paragraph 19.) Lambda antibodies are found in two-thirds of light chain amyloidosis (AL amyloidosis) cases, whereas kappa light chains mediate greater than 85% of Light-Chain Deposition Disease (LCDD), a distinct protein deposition disease. (*Id.*) The character and rate of the catabolic processes involved in the clearance of kappa and lambda light chains are different, and the difference in the structure of amyloid fibrils (fibrilar) and the LCDD deposits (amorphous) further reflects the difference in the general structure of kappa and lambda light chains. (*Id.* at paragraph 20).

Because of distinctions between kappa and lambda light chains, the expression of kappa light chains on the B-cell surface as purportedly described in the Raison publication does not predictably suggest that free *lambda* light chain is localized on the surface of, e.g., myeloma cells. (*Id.* at paragraphs 22 and 23.) The Uhr patent's disclosure relating to intact antibodies displayed on the surface of tumor cells does not cure the deficiencies of the Raison publication. Intact immunoglobulin, which is found on both normal and tumor cells (unlike LMA), differs structurally from free lambda light chain, and its localization on the cell surface does not imply that *free* lambda light chain is localized on myeloma cells. Similarly, the Abe reference's mere disclosure of antibodies against free lambda light chain does not suggest LMA as a target for the destruction of lymphoid cells. Thus, the Uhr patent, the Raison publication, and the Abe reference, alone or in any combination, fail to render

obvious a method for treating a B-cell disorder, inhibiting or killing lymphoid cells, or treating a cell population for autologous hematopoietic cell transplantation using an anti-LMA antibody or LMA ligand.

Likewise, in the absence of a predictable teaching that free lambda light chain is displayed on the surface of hematopoietic cells, the cited references do not render obvious the anti-LMA antibody of claims 43 and 47 or the pharmaceutical composition of claim 48. As noted by Dr. Jennings in the Rule 132 Declaration, no normal biological function was attributed to free lambda light chain prior to the instant application. (Rule 132 Declaration at paragraph 17.) Thus, one of ordinary skill would not have been motivated to conjugate a cytotoxic moiety, biological modifier, or detectable label to an anti-LMA antibody. (*Id.* at paragraph 17.) Accordingly, the subject matter of claims 43-48 is not obvious in view of the cited references under Section 103.

With respect to claims 39-42, 45, and 46, the Office contends that the Rubin publication discloses therapeutic use of chimeric antibodies, labeled anti-tumor antibodies, and antibody conjugates, and that "[a] routineer would have treated the autologous cell transplant recipient with the antilambda antibody to kill tumor cells present in the recipient" (Office Action, page 6). However, the Rubin publication, like the Uhr, Raison, and Abe references, fails to teach or suggest that surface-localized *free* lambda light chain exists, much less that free lambda light chain is a target for localizing lymphoid cells in a subject, treating a B-cell disorder, inhibiting or killing lymphoid cells, or treating hematopoietic cells prior to transplantation. The references, alone or in combination, fail to render obvious the presently claimed subject matter.

In support of its position, the Office cited *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), which states that "if a technique had been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve a similar device in the same way, using the technique is obvious unless its actual application is beyond his or her skill." The rationale relied upon by the Office requires that the results of applying the "improvement" would have been predictable to one of ordinary skill in the art. M.P.E.P. § 2143. As explained above, the ordinarily skilled artisan would not have predicted that free lambda light chain is expressed on the surface of lymphoid cells. Thus, administering an

anti-LMA antibody to a subject to, e.g., treat a B-cell disorder, would have been unpredictable prior to the instant application. Accordingly, the rationale articulated in *KSR International Co. v. Teleflex Inc.* cannot be used to support a conclusion that the claims would have been obvious. 72 Fed. Reg. at 57529 ("If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art."). The Office has presented no alternative rationale supporting its position. Accordingly, the rejection should be withdrawn.

For the reasons set forth above, the subject matter of claims 28-48 is patentable over the cited art, and the Rubin publication, and the rejection under Section 103 should be withdrawn.

V. Conclusion

The application is considered to be in good and proper form for allowance, and the examiner is respectfully requested to pass this application to issue.

This paper is accompanied by petition for a three-month extension of time with the required fee. The commissioner is authorized to charge any additional fees due in connection with this filing to Marshall, Gerstein and Borun, LLP deposit account number 13-2855, under order no. 29729/38914.

Dated: December 13, 2010

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